ON INTRACRANIAL THROMBOSIS AS THE CAUSE OF DOUBLE OPTIC NEURITIS IN CASES OF CHLOROSIS, BY C. O. HAWTHORNE, M.D., M.R.C.P.

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With compliments

ON INTRACRANIAL THROMBOSIS AS THE CAUSE OF DOUBLE OPTIC NEURITIS IN CASES OF CHLOROSIS.[1]

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The object of this communication is to support the suggestion that double optic neuritis occurring in patients the subjects of chlorosis is due to intracranial thrombosis. The evidence I have to submit, so far as my personal observation goes, consists of the facts of a single case, but these, if not absolutely conclusive, are at least highly significant, and certainly add weight to testimony having a similar direction and derived from other sources. The patient was a girl, aged 17 years, distinctly, though not extremely, anæmic, and admitting some measure of menstrual irregularity. She was free from all evidence of disease in the thoracic and abdominal viscera, and ultimately made a complete recovery. In short, with the exception of two facts yet to be related, there was nothing to separate the case from the numerous examples of chlorosis seen by every practitioner. These two facts were diplopia and double optic neuritis. The double vision was of sudden and recent origin (fourteen days), and was found to depend on a paralysis of the external rectus muscle of the right eyeball. Visual acuity was normal, there was a slight degree of hypermetropia, and the ophthalmoscope revealed considerable optic neuritis in each fundus. Still later there were retinal changes in each macular region, with some depreciation of the visual power. After a few weeks' treatment by rest and the administration of iron, normal vision was regained, the optic neuritis subsided, and the ocular paralysis entirely disappeared.

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[1] A Paper read before the Ophthalmological Society of the United Kingdom and reprinted from the British Medical Journal, February 8, 1902.

The question now proposed to be raised is whether the occurrence of an ocular paralysis in association with double optic neuritis in a chlorotic girl, throws any light on the causation of the optic neuritis known to occur in a small, but recognised, proportion of patients free from all evidences of disease other than chlorosis. The proposition that it does so can scarcely be argued unless it first be admitted that the two events—the ocular paralysis and the optic neuritis—were, if not certainly, at least in all probability, the results of a common cause. The theoretical possibility that they may have arisen from different causes must, perhaps, be allowed; but the balance of evidence inclines strongly in the opposite direction. Thus, they appeared at or about the same time, and they both declined together. There is one event—an intracranial thrombosis—competent to produce them. This event is, in the circumstances, a probable one. When a simple cause is adequate to explain the phenomena observed, the *onus probandi* lies with those who affirm a more complex causation. In a case of admitted intracranial lesion, the occurrence of the two events now in question, so far from extending or complicating the diagnosis, would be referred without doubt to a common disturbing influence. It is reasonable to apply the same canons of interpretation to the case of chlorosis now under consideration, and to conclude that the ocular paralysis and the optic neuritis which were present, took origin in a common cause. That cause, it is suggested, was a cerebral thrombosis. And from this conclusion it is proposed to argue that when optic neuritis—unattended by an ocular paralysis or other evidence of cerebral disturbance—occurs in chlorosis, it also is to be referred to a cerebral thrombosis.

Before presenting the evidence in favour of these propositions, it may be observed that certain alternative suggested causes of the optic neuritis of chlorosis fail altogether to explain the present case unless upon the supposition that the optic neuritis and the ocular paralysis were due to different causes, which, it has already been submitted, is highly improbable. One of these suggestions—and, in consideration of its distinguished author, one to be received with every deference—is that the optic neuritis of chlorosis is due to the conjoined influence of hypermetropia and the abnormal state of the blood. Now even though it be allowed that these may cause

optic neuritis, they can hardly explain the development of a unilateral ocular paralysis, sudden in appearance, and of temporary duration. Similarly, menstrual suppression—which, however, only existed in the present case in a very partial sense—offers no interpretation of the paralysis. The same is probably true of toxic material introduced from the intestine or other source into the blood. It may further be remarked that hypermetropia is a relatively common condition in young women, and that many chlorotic patients suffer from amenorrhœa; whilst optic neuritis in these patients is a very rare event. If any one of the above-mentioned views is correct, it follows, either that in different cases of chlorosis optic neuritis arises from different causes, or that in the present instance there was one cause for the paralysis and another for the neuritis. On the other hand, it can be shown that intracranial thrombosis may occur in chlorosis, and that it is capable of producing both optic neuritis and a sixth nerve paralysis.

That thrombosis is to be numbered among the possible complications of chlorosis is quite beyond doubt. It is, like optic neuritis, a rare and exceptional event, but it occurs with sufficient frequency to show that the disease includes, at least in a proportion of cases, some factor which tends to intravascular blood clotting. Professor W. H. Welch has collected eighty-two cases, and believes more could be gathered by "thorough overhauling of medical books and periodicals." No fewer than seventy-eight out of the eighty-two were examples of venous thrombosis, and of these the cerebral sinuses were involved in thirty-two instances. "Chlorosis must be given," writes Professor Welch, "a leading place among the causes of spontaneous thrombosis of the cerebral veins and sinuses in women."

Now it is certain that double optic neuritis may be included among the symptoms of such thrombosis. Cases supporting this statement are attested by such authorities as Professor Clifford Allbutt, Sir Dyce Duckworth, Professor Osler, Dr. Buzzard, Dr. A. Brayton Ball, Dr. Lee Dickinson, and others. It is no doubt true that from some of the most extreme cases of cerebral thrombosis optic neuritis has been absent. But equally it is sometimes absent from cases of cerebral tumour. Yet no one, on account of these negative experiences, declines to admit tumour to a place

among the causes of optic neuritis; and the evidence for thrombosis is hardly, if at all, less strong.

Again, it is not difficult to accept thrombosis of the cerebral veins or sinuses as an agent competent to cause an ocular paralysis. It may undoubtedly produce, as in some of the cases above alluded to, widespread motor disturbances, either convulsive or paralytic, on one or both sides of the body. And in some of the reported cases the paralysis involved the ocular movements. Even apart from actual demonstration of this point, it is reasonable to conclude that, given a limited thrombosis, one of its effects may be paralysis within a limited area. It is fair also to point out that if such cases occur, it is not to be expected that *post-mortem* evidence will be available, for whilst extensive cerebral thrombosis often proves fatal, slight cases may readily make a complete, and possibly a rapid, recovery. Nor is it unreasonable to urge that the slighter cases may be accompanied by optic neuritis; for, as it is certain that the occurrence or non-occurrence of optic neuritis in cases of tumour is independent of the size of the tumour, so it is probable that in cases of thrombosis the development or otherwise of optic neuritis depends on some factor other than the extent of the thrombosed area. It has already been remarked that in some instances of extensive thrombosis there is no optic neuritis. The parallel with the conditions which obtain in cerebral tumours may possibly be completed by the development of neuritis when the thrombosis is of but limited extent. Neither the absence of *post-mortem* evidence, nor the suggestion that a limited thrombosis is unlikely to cause optic neuritis, can be regarded as fatal to the hypothesis that, in a case of chlorosis with double optic neuritis and an ocular paralysis, both of these events were due to a cerebral thrombosis.

The argument regarding the case now in question may therefore be briefly presented as follows: The simultaneous occurrence of the optic neuritis and the sixth nerve paralysis suggests a common origin; the nature and temporary duration of the two events makes it difficult to imagine any single cause capable of producing them other than an intracranial lesion; an intracranial thrombosis may certainly produce them; intracranial thrombosis is a recognised possibility in chlorosis; the patient is the subject of chlorosis;

therefore it may be concluded with a considerable measure of confidence that both the optic neuritis and the sixth nerve paralysis were due to intracranial thrombosis.

From such a conclusion it is but a step to the proposition that thrombosis is probably the cause of optic neuritis when this occurs in chlorosis apart from other incidents having a possibly cerebral origin. The invitation to take that step is rendered more pressing when it is perceived that from cases of chlorosis with optic neuritis and severe cerebral disturbances proved by necropsy to be due to intracranial thrombosis, a series of cases of gradually diminishing severity can be traced downwards to the instances in which chlorosis is complicated by optic neuritis as the single event having thrombosis as a possible interpretation. At one extreme are fatal cases in which delirium, coma, hemiplegia, and double optic neuritis have been shown by necropsy to be associated with thrombosis of the intracranial veins and sinuses; following these are instances of less severe, though considerable, cerebral disturbance, with optic neuritis and evidences of thrombosis in the veins of the limbs or other parts of the body; these are succeeded by examples of chlorosis with headache more than usually extreme, more or less vomiting, and an ocular paralysis; next may be placed cases—like the one reported with this paper—in which the symptomatic disturbances other than those common in chlorosis are restricted to an ocular paralysis and double optic neuritis; and last of all are those in which the optic neuritis is the sole unusual event. Such a gradation is certainly an impressive one, and may reasonably be presented in support of the proposition that in these different groups we have to deal with different degrees of severity and extent of one and the same pathological process, and that the pathological event underlying them all is a thrombosis of the intracranial sinuses and veins.

A case in which retinitis in a chlorotic girl was present only in one eye may here be mentioned. It is quoted from Knies in Norris and Oliver's "System of Diseases of the Eye," vol. iv., p. 535. The appearances were very similar to those seen in albuminuric retinitis, and occasionally also in tumour; the condition lasted for more than six months and disappeared without leaving a trace of its existence. To believe that a monocular retinitis could

be directly occasioned by a toxic or other abnormal state of the blood is certainly difficult, though not perhaps impossible. On the other hand, thrombosis may be advanced as a more probable explanation. In cases of tumour optic neuritis is now and again restricted to one eye, and a thrombus in a cerebral sinus or vein may conceivably act in a similar manner.

Another source of evidence supporting the thesis here affirmed may be found in occasional experiences recorded by aural surgeons. Though it is held by some authorities that optic neuritis may be produced by suppurative disease of the middle-ear without the occurrence of any intracranial complication, the discovery of this symptom in the course of a case of tympanic disease undoubtedly generally means a serious development within the skull. It may be due to abscess; it may depend on meningitis; or, again, it may be associated with sinus thrombosis. Certainly it is not always due to abscess, for many patients with middle-ear disease and optic neuritis make a complete recovery apart from the surgical measures which an abscess requires. The exclusion of meningitis cannot be so confidently asserted, at least in cases of recovery, because meningitis, more or less extensive, may obviously readily develop in any case of suppurative disease of the middle-ear which has induced intracranial changes. But, subject to this qualification, there is a considerable body of evidence in favour of the view that thrombosis is the event to which the development of optic neuritis must usually be credited. Newton Pitt, in his Goulstonian Lectures (1890), analyses fifty-seven fatal cases of ear disease and of the complications which led to death, and concludes that optic neuritis is more suggestive of sinus thrombosis than of abscess or meningitis. He says, indeed, that optic neuritis is rarely due to meningitis, and that it is infrequent in uncomplicated cases of abscess. Quite a number of cases of ear disease with optic neuritis are on record in which the removal of clot from the lateral sinus has been followed by disappearance of all the symptoms, and it has been observed in some of these that the neuritis was an early indication of cerebral developments, whereas meningitis is admitted to be a relatively late complication of sinus thrombosis. There are other cases in which the application of operative measures to the mastoid, without opening the skull, has been followed by subsidence

of the optic neuritis, and though it cannot be positively affirmed that in these instances there was no meningitis, thrombosis is at least an equally probable explanation. Further, in some cases of middle-ear disease the optic neuritis has been associated with paresis of some of the ocular muscular mechanisms. In one case, described by Marmaduke Sheild, there were early ocular symptoms including optic neuritis and dilatation and fixation of one pupil. Operation was declined, and the necropsy showed septic thrombosis of the right lateral and cavernous sinuses with a meningitis of quite recent date. Clarence A. Veasey records a successful operation in a case of lateral sinus thrombosis in which the temperature was but little elevated, and in which there was optic neuritis, and later, paralysis of the right external rectus muscle, the two last features becoming for a time more marked after operation. This last statement, more especially when taken with the fact that the operation immediately relieved such symptoms as headache and vomiting, may be claimed as valuable evidence in favour of the suggestion that the neuritis and the ocular paralysis were the results of intracranial thrombosis. This conclusion is also supported by a case reported by Mayo Collier, in July, 1901, at the British Laryngological Society. The patient was a young woman, the subject of tympanic disease, in whom there had developed optic neuritis and paralysis of each sixth nerve, these being the only evidences of intracranial mischief. A radical operation was performed on the mastoid and middle-ear, but the skull was not opened. Yet three weeks after operation, though the neuritis and paralysis had not disappeared, no further signs of cerebral disturbance had developed, and in the course of the discussion on the case at least one parallel instance was described in which the patient made a complete recovery. Intracranial thrombosis offers itself as at least a possible explanation of all the facts of these cases. It is an admitted complication of middle-ear disease. It may undoubtedly produce optic neuritis. There is reason to believe that it may also cause various ocular paralyses. When these two events occur together in a case of tympanic disease it is surely reasonable to suggest thrombosis as probable in the circumstances, and competent as an explanation of the existing symptoms.

Thus it appears that chlorosis and middle-ear disease may each occasionally be complicated by intracranial thrombosis. In each of them, too, are found instances in which optic neuritis develops. With this there is sometimes an ocular paralysis. Thrombosis may explain these symptoms. It would be difficult to find any other cerebral event common to both chlorosis and disease of the middle-ear which will explain them. But if thrombosis will explain the optic neuritis and ocular paralysis when these are associated, and if, as sometimes happens, the optic neuritis occurs apart from paralysis, is it not probable that here also the pathological cause is an intracranial thrombosis? The series of events found in the intracranial complications of middle-ear disease may in this way be presented to support the proposition that the optic neuritis of chlorosis is the result of thrombosis within the cranial cavity.

There is yet a third class of cases which may be mentioned in the discussion of this subject, namely, those in which optic neuritis develops after a considerable hæmorrhage. Standing alone they appear as puzzles. But it seems worth considering whether the change in the quality of the blood, and the weakening effect on the heart produced by the hæmorrhage, may not possibly lead to thrombosis in the cerebral veins and sinuses, where for anatomical reasons the blood current is naturally sluggish. In such cases, though the bulk of the blood is soon restored by absorption from the alimentary canal and the tissues, and by diminution of the excretion of water by the kidneys, the restoration of the corpuscles is a much slower process. Hence, for some time, the plasma is watery, and the corpuscles deficient (Coats)—a state of matters by no means unlike the conditions which exist in chlorosis. It can hardly be doubted that these conditions favour the occurrence of thrombosis, and as this may undoubtedly cause optic neuritis, it may at least be said that as optic neuritis sometimes occurs after an acute hæmorrhage, that is when thrombosis is a possibility, such an occurrence strengthens the argument for thrombosis as a cause of the optic neuritis recognised as an occasional event in chlorotic women.

Concerning the manner in which thrombosis may be supposed to lead to such results as are here discussed, it is not necessary to assume that to produce optic neuritis a thrombus must be situated

so as to mechanically interfere with the venous return from the eyeballs. A thrombus once formed is for all practical purposes a tumour, in the sense that it is a "foreign body" or "adventitious product" within the skull. And whatever conflict of opinion may yet exist regarding the manner in which cerebral tumours cause optic neuritis, it is certain that neither the size nor the position of the tumour is the determining factor. A thrombus in this respect doubtless behaves in the fashion set by other forms of "tumour." Again, it must be remembered that the formation of a thrombus may be followed by consequences which involve pathological changes in the nervous tissues themselves, such as hæmorrhage, œdema, or softening; and that any one of these, if favourably situated, may readily interfere with the activity of the centre or trunk of one or other of the cranial nerves, and may, indeed, be a further agency in the production of optic neuritis. In short, thrombosis as a possible cause of cerebral symptoms must be considered together with the changes in the nerve elements which it produces in its neighbourhood.

If these views are correct, certain practical conclusions in reference to treatment follow. The thrombosis which occurs in chlorosis is in all probability an aseptic process. One of the factors in its causation is doubtless a sluggish state of the circulation, due to cardiac weakness. The immediate risks are (1) that the thrombus will grow over a larger area; and (2) that a portion will become detached and lead to embolism. To prevent the latter result, complete rest is imperative; but it is necessary to take steps to prevent the policy of rest reducing the vigour of the circulation to such an extent as to favour the extension of the thrombus. Hence, it would seem wise in cases of chlorosis acccompanied by optic neuritis to supplement the administration of iron by cardiac tonics, as digitalis, and by diffusible stimulants, more particularly ammonia. When a passive thrombus has been fully formed, its tendency is not to detachment, but to organisation; and thus, as soon as the above measures have afforded a reasonable guarantee that further extension of the thrombus is improbable, complete rest should no longer be enforced. The indication now is to increase the vigour of those vital processes on which organisation and practical removal of the thrombus depend. Among these is

a reasonable amount of exercise which, the fear of embolism having been reduced to a minimum, may now be safely and beneficially ordered and pursued.

Notes and References.

The original cases of optic neuritis in chlorosis recorded by Sir William Gowers, together with a statement of his views regarding the influence of hypermetropia in association with the abnormal state of the blood as a factor in the causation of the neuritis, are to be found in his "Medical Ophthalmoscopy," and in the *British Medical Journal*, 1881, vol. i., p. 796. A paper by Saundby and Eales, in which the influence of hypermetropia in the same direction is discussed, appeared in the *Ophthalmic Review*, September, 1882; see also Saundby in *Birmingham Medical Review*, November, 1885. Sir William Broadbent (*Trans. Ophthal. Society*, 1880-81, p. 108) has reported two cases of young women in whom optic neuritis was associated with amenorrhœa; one of these was fatal, and "the only morbid appearance in the brain was effusion into the ventricles." Cases of double optic neuritis with a similar *post-mortem* result are included in a paper by Williamson and Roberts (*Lancet*, 1900, vol. i., p. 1350). Examples of severe cerebral disturbance and optic neuritis in chlorosis with intracranial thrombosis on necropsy are recorded by Bristowe ("Clinical Lectures and Essays on Disease of the Nervous System"), Sir Dyce Duckworth (*British Medical Journal*, 1896, vol. i., p. 149), Lee Dickinson (*Clinical Society's Trans.*, 1896, vol. xxix., p. 63), and A. Brayton Ball (*Trans. Assoc. of American Physicians*, 1889, vol. iv., p. 57). Cases with similar symptoms terminating in recovery have been reported by Bristowe (*loc. cit.*), and by Buzzard (*British Medical Journal*, 1896, vol. i., p. 150). Instances of fatal cerebral thrombosis without optic neuritis are noted by Sir R. Douglas Powell (*Lancet*, 1888, vol. ii., p. 1124), and by Stephen Mackenzie (*Practitioner*, February, 1898); see also Brayton Ball's collected cases. Professor Welch's article, in which the whole question of intracranial thrombosis in chlorosis is discussed, is in Clifford Allbutt's "System of Medicine," vol. vi., p. 200, and a list of published cases is given at p. 227. Clifford Allbutt himself deals with the question in vol. v., p. 508, and in vol. vii., p. 574, James Taylor refers to the probability that some cases of optic neuritis originate in thrombosis in the cerebral veins or sinuses. Instances of double optic neuritis with more or less cerebral disturbance in patients with chlorosis are recorded by Wardrop Griffith (*British Medical Journal*, June 9, 1888), Burton-Fanning (*Ibid.*, 1894, vol. i., 1354), and Crawford Thomson (*Ibid.*, 1073), the latter including a case in which there was diplopia. One of Lee Dickinson's patients, in addition to optic neuritis and hemiplegia, had a "varying squint," and in another there was inequality of the pupils. In one of Griffith's cases the patient was chlorotic and had extreme neuro-retinitis without any other evidence of intracranial lesion. While under treatment she fell on the ice and struck her head. Three weeks after this she became delirious, with febrile temperatures and dilated pupils. The necropsy showed a tumour of the occipital lobe, with some evidences of meningitis at the base of the brain—an illustration that chlorosis in association with double optic neuritis does not exclude cerebral tumour from the diagnosis. An instance of double optic neuritis and sixth nerve paralysis, practically identical with the one on which the present paper is founded, is reported by Diabella (quoted in *Lancet*, September 19, 1896). Another is described by Sir William Gowers (*Transactions*

of the Ophthalmological Society, 1880-81, p. 115); the symptoms in this instance included occipital pain and vomiting, and the diagnosis suggested was a transient localised meningitis. Several of the cases reported as instances of optic neuritis in chlorosis have also suffered from severe pain in the head and from vomiting. Burton-Fanning (*loc. cit.*) relates such a case, and suggests that the absence of fever, &c., excludes basal meningitis from the diagnosis; he proposes increased intracranial pressure from œdema of the brain as the probable cause. It may be suggested that thrombosis is adequate to explain all these facts. The rarity of sinus thrombosis as a condition producing severe symptoms in anæmia may be judged from the fact that Byrom Bramwell ("Anæmia and Diseases of the Ductless Glands") met with no example in an experience of 314 cases of chlorosis. The references to cases of middle-ear disease with ocular symptoms are as follows: Newton Pitt (*British Medical Journal*, 1890, vol. i., p. 648, *et seq.*); Marmaduke Sheild (*Archives of Otology*, 1892, p. 283); Whiting (*Ibid.*, 1898, No. 6); Clarence A. Veasey (*Ophthalmic Record*, June, 1899); Mayo Collier (*Transactions of the Laryngological and Otological Society of Great Britain*, July, 1901); Macewen ("Pyogenic Diseases of the Brain and Spinal Cord"); Barr ("Manual of Diseases of the Ear," Second Edition); the last-named mentions paralysis, either of the third or sixth nerve, as a result of thrombosis of the cavernous sinus. With these references may be associated instances in which middle-ear disease was complicated by an ocular paralysis without optic neuritis. Two cases of this character have been recorded by Professor F. de Lapersonne (*Medical Review*, September, 1901, p. 623). A further reference of interest in connection with the argument advanced in the present paper is an account of a case of enteric fever in which a unilateral third nerve paresis developed comparatively early, and the patient at a later date suffered from thrombosis of the right femoral vein. No other obvious cerebral disturbance accompanied the paresis, and lumbar puncture gave a clear fluid, free from organisms. The possibility of a limited meningitis must of course be accepted, but in the circumstances thrombosis can hardly be denied a hearing. The case is recorded by Chas. P. Emerson, in the *Johns Hopkins Hospital Reports*, 1900, vol. viii., p. 897.

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